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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LU, FRANK WEI MIN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,950	RADTKEY ET AL.	
	Examiner	Art Unit	
	Frank W. Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-14,17-25 and 27* is/are pending in the application.

4a) Of the above claim(s) *10-14 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-9,17-20,22-25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/5/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

1. Applicant's response to the office action filed on July 5, 2006 has been entered. The claims pending in this application are claims 1, 5-14, 17-25, and 27 wherein claims 10-14 and 21 have been withdrawn due to species election. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the response filed on July 5, 2006.

Drawings

2. The drawings submitted on August 1, 2006 have been accepted by the office.

Specification

3. The amended specification in page 29, last paragraph bridging to page 30, first paragraph filed on July 5, 2006 has not been entered because it does not list any marked change. See 37 CFR 1.121 (b).

Claim Objections

4. Claim 1 is objected to because of the following informality: "and" between the second providing step and the second hybridizing step should be changed to the position between the second hybridizing step and the detecting step.

5. Claim 23 or 27 is objected to because of the following informality: there should be a word "and" between providing step and hybridizing step.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. New Matter

Claims 1, 5-9, 17-20, 22-25, and 27 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The recitation "detecting a genetic marker in a patient sample nucleic acid" is added to the newly amended independent claim 1. Although the specification describes detecting members of a set of polymorphisms in a patient sample by hybridizing a discriminators with the patient sample wherein the discriminator is capable of binding with the at least one unblocked loci (eg., see original filed claim 1), the specification fails to define or provide any disclosure to support detecting a genetic marker in a patient sample by hybridizing a discriminators with the patient sample wherein the discriminator is capable of binding with the at least one unblocked loci as recited in claim 1 because "genetic marker" can be defined as an identifiable substance that is associated with a normal or an abnormal gene (see attachment for "genetic marker") and is much broader than "polymorphism". Furthermore, in applicant's remarks filed on July 5, 2006, applicant does not indicate which part in the specification supports such claim recitation.

MPEP 2163.06 notes "IF NEW MATTER IS ADDED TO THE CLAIMS, THE EXAMINER SHOULD REJECT THE CLAIMS UNDER 35 U.S.C. 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION REQUIREMENT. *IN RE RASMUSSEN*, 650 F.2D 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application." MPEP 2163.06 further notes "WHEN AN AMENDMENT IS FILED IN REPLY TO AN OBJECTION OR REJECTION BASED ON 35 U.S.C. 112, FIRST PARAGRAPH, A STUDY OF THE ENTIRE APPLICATION IS OFTEN NECESSARY TO DETERMINE WHETHER OR NOT "NEW MATTER" IS INVOLVED. *APPLICANT SHOULD THEREFORE SPECIFICALLY POINT OUT THE SUPPORT FOR ANY AMENDMENTS MADE TO THE DISCLOSURE*" (emphasis added).

8. Scope of Enablement

Claims 1, 24, and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the method recited in claim 1 for detecting a genetic marker in a patient sample nucleic acid, does not reasonably provide enablement for using the method recited in claim 1 for detecting any kind of genetic disease such as cystic fibrosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance in the specification to show that the method recited in claim 1 can be used for detecting any genetic disease such as cystic fibrosis. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether the method recited in claim 1 can be used for detecting any kind of genetic disease such as cystic fibrosis.

Claim 1 is directed to a method for detecting a genetic marker in a patient sample nucleic acid. Claims 24 and 25 further limit that the genetic marker in claim 1 is indicative of a genetic disease such as cystic fibrosis. Since at least one blocker and the detectable discriminator recited in claim 1 are not specific for a genetic disease such as cystic fibrosis, in view of claims 24 and 25, it is unclear how at least one blocker and the detectable discriminator recited in claim 1 which are non-specific for a genetic disease such as cystic fibrosis can be used for detecting a genetic disease such as cystic fibrosis.

With above unpredictable factor, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether the method recited in claim 1 can be used for detecting any kind of genetic disease such as cystic fibrosis using at least one blocker and a discriminator which are non-specific for a genetic disease such as cystic fibrosis.

Response to Arguments

In page 23, first paragraph of applicant's remarks, applicant argues that "[A]pplicants have amended claim 1 to specify a 'method for detecting a genetic marker' by 'detecting the presence of the discriminator.' Furthermore, claim 24 has been amended to specify that the

'genetic marker is indicative of a genetic disease.' Claim 25 specifies that the genetic disease is cystic fibrosis. Applicants respectfully assert that there is ample support in the specification at, e.g., page 9, line 20 - page 11, line 18, page 45, line 22 - page 66, line 16, and Tables 11 and 12. Therefore, Applicants respectfully request withdrawal of the rejections and reconsideration of the claims as amended".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Although page 9, line 20 - page 11, line 18, page 45, line 22 - page 66, line 16, and Tables 11 and 12 of the specification describe detection of the cystic fibrosis-related mutations, since at least one blocker and the detectable discriminator recited in claim 1 are not specific for a genetic disease such as cystic fibrosis, in view of claims 24 and 25, it is unclear how at least one blocker and the detectable discriminator recited in claim 1 which are non-specific for a genetic disease such as cystic fibrosis can be used for detecting a genetic disease such as cystic fibrosis. Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1, 5-9, 17-20, 22-24, and 27 are rejected under 35 U.S.C. 102(e) as being anticipated by Nerenberg *et al.*, (US Patent No. 6,468,742 B2, filed on April 12, 1999).

Regarding claim 1, since there is no definition in the specification for "genetic marker" and it is known that "genetic marker" can be defined as an identifiable substance that is associated with a normal or an abnormal gene (see attachment for "genetic marker"), the sequence of the single stranded target nucleic acids of interest that is complementary to at least one reporter oligonucleotide taught by Nerenberg *et al.,* is considered as a genetic marker (an identifiable substance that is associated with a normal or an abnormal gene). Therefore, Nerenberg *et al.,* teach a method for detecting a genetic marker in a patient sample nucleic acid, comprising the steps of: providing patient sample nucleic acids containing multiple loci (ie., the single stranded target nucleic acids of interest) at a site (ie., the electronically addressable microchip); providing at least one blocker (ie., the at least one stabilizer oligonucleotide) that is complementary to at least one loci (ie., the region of the target nucleic acid of interest that is complementary to the at least one stabilizer oligonucleotide) of the multiple loci contained in the patient sample nucleic acid, hybridizing the at least one blocker with the patient sample nucleic acid wherein at least one loci containing the genetic marker is unblocked; providing a detectable discriminator (ie., the at least one reporter oligonucleotide) that is capable of binding with the at least one unblocked loci; hybridizing the discriminators with the at least one unblocked loci of the patient sample; and detecting the genetic marker by detecting the presence of the discriminator (see abstract, columns 5-9, claims 1-125 in columns 27-38, and Figures 2 and 4).

Regarding claims 5, 6 and 22, since Nerenberg *et al.,* teach that the capture sites in column 1 and 2 of the microchip receive a Hemochromatosis wild type and Factor V mutant while the sites in column 4 and 5 of the microchip are targeted with both Hemochromatosis and Factor V Heterozygotes, reporting is done sequentially, first with the allele-specific

Hemochromatosis reporters (SEQ ID Nos. 11 and 12) and then the allele-specific Factor V reporters (SEQ ID Nos. 16 (CGCCTGTCCAG-CR6G) and 17 (TGCCTGTCCAG-Far Red), and before Factor V reporters are passively hybridized, all remaining Hemochromatosis reporters are stripped from the microarray (see column 12, lines 14-45, column 20, lines 1-30, and claims 1, 16, and 17 in columns 27-29), Nerenberg *et al.*, disclose that different blockers (ie., allele-specific Hemochromatosis reporters and the allele-specific Factor V reporters) are provided to different sites (ie., the sites of columns 1, 2, 4, and 5) as recited in claim 5, the site comprises a site of an actively addressable electronic microarray as recited in claim 6, and the multiple patient samples (ie., Hemochromatosis wild type, Factor V mutant, and Hemochromatosis and Factor V Heterozygotes) are provided on multiple sites (ie., columns 1, 2, 4, and 5) of the microarray as recited in claim 22.

Regarding claim 7, Nerenberg *et al.*, teach that the addressable electronic microarray includes a permeation layer (see column 12, lines 49-67, column 13, lines 1-3, and Figures 1A and 1B).

Regarding claims 8 and 9, Nerenberg *et al.*, teach that the patient sample is amplified as recited in claim 8 wherein the amplification includes polymerase chain reaction (PCR) as recited in claim 9 (see claims 1 and 22-29 in columns 27-30).

Regarding claim 17, Nerenberg *et al.*, teach that at least two loci (ie., the sites that two reporter probes 43 and 44 hybridize to) are unblocked (see column 21, lines 53-62 and Figures 4a and 4b).

Regarding claim 18, Nerenberg *et al.*, teach performing a screening step (ie., analyzing unknown hemochromatosis samples) (see column 19, lines 38-65).

Regarding claims 19 and 20, Nerenberg *et al.,* teach that the patient sample nucleic acid comprises multiple segments containing different loci (ie., the sites that two reporter probes 43 and 44 hybridize to) as recited in claim 19 wherein the multiple segments containing different loci are affixed to the same site (ie., the site on the microchip) as recited in claim 20 (see column 21, lines 53-62 and Figures 4a and 4b).

Regarding claim 23, Nerenberg *et al.,* teach providing a labeled amplification control (ie., another reporter oligonucleotide such as 43 in Figure 4b) that is capable of binding with the patient nucleic acid sample; and hybridizing the labeled amplification control to the patient nucleic acid sample (see Figure 4b and column 30, claim 31).

Regarding claim 24, Nerenberg *et al.,* teach that the genetic marker (ie., the sequence of the single stranded target nucleic acids of interest that is complementary to at least one reporter oligonucleotide taught by Nerenberg *et al.,* eg., the nucleotide sequences including * in nucleic acid 40 of Figure 4) is indicative of genetic diseases (see column 9, lines 43-46 and column 13, lines 36-49).

Regarding claim 27, Nerenberg *et al.,* teach providing a stabilizer (ie., probe 46) that is capable of binding with the patient nucleic acid sample (ie., nucleic acid 40) adjacent the at least one discriminator (ie., the probe 44) and hybridizing the stabilizer to the patient nucleic acid sample (see Figure 4b).

Therefore, Nerenberg *et al.,* teach all limitations recited in claims 1, 5-9, 17-20, 22-24, and 27.

Response to Arguments

In page 24, second paragraph bridging to page 25, first paragraph of applicant's remarks, applicant argues that "[A]pplicants respectfully assert that Nerenberg does not teach or suggest 'at least one blocker that is complementary to at least one loci of the multiple loci contained in the patient sample nucleic acid,' as required in amended claim 1. Although the stabilizer described in Nerenberg is complementary to a portion of the amplification product, it is not complementary to 'at least one loci of the multiple loci contained in the patient sample nucleic acid.' As stated in Nerenberg, '[t]he stabilizer oligomer 33 is generally a 30-mer that is 100% complementary to both wild type and mutant alleles. This stabilizer directly abuts the polymorphism site on the target amplicon such that when a perfectly matched mutant reporter 34 or wild-type 35 is added to the system, base-stacking will be present.' (emphasis added, Col. 16, lines 30-36). Because the stabilizer 'directly abuts' the loci, it is not complementary to the loci, but rather is complementary to a sequence near the loci. Additionally, because the stabilizer is '100% complementary to both wild type and mutant alleles,' the stabilizer must not be hybridizing with the portion of the amplification product that contains the loci (i.e., the polymorphism that makes the mutant different from the wild type). As stated previously, the stabilizer is hybridizing with a portion of the amplification products that is common to both".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since at least one stabilizer oligonucleotide taught by Nerenberg *et al.,* comprises a sequence complementary to at least a portion of the target nucleic acid of interest (see claim 1 in columns 27 and 28), Nerenberg *et al.,* do teach at least one blocker that is complementary to at least one loci (ie., the region of the target nucleic acid of

interest that is complementary to the at least one stabilizer oligonucleotide) of the multiple loci contained in the patient sample nucleic acid. Second, the office action does not indicate that the polymorphism site in column 16, lines 30-36 of Nerenberg *et al.,* is at least one loci of the multiple loci contained in the patient sample nucleic acid as argued by applicant.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nerenberg *et al.,* as applied to claims 1, 5-9, 17-20, 22-24, and 27 above, and further in view of Song *et al.,* (US Patent NO. 6451,526, filed on January 15, 1999).

The teachings of Nerenberg *et al.,* have been summarized previously, *supra.*

Nerenberg *et al.,* do not disclose that the genetic disease is cystic fibrosis as recited in claim 25.

Song *et al.,* suggest that different target nucleic acids including ApoE4, cystic fibrosis, Factor V, and HFE (hemochromotosis) genes as well as oncogenes such as the RET proto-oncogene can be used for mutation detection (see column 5, last paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art

at the time the invention was made to have performed the method recited in claim 25 wherein the genetic disease is cystic fibrosis in view of the patents of Nerenberg *et al.,* and Song *et al.*. One having ordinary skill in the art would have been motivated to do so because and Song *et al.,* suggest that different target nucleic acids including ApoE4, cystic fibrosis, Factor V, and HFE (hemochromotosis) genes as well as oncogenes such as the RET proto-oncogene are used for mutation detection (see column 5, last paragraph) and the simple replacement of one kind of target nucleic acid (ie., the target nucleic acid taught by Nerenberg *et al.,*) from another kind of target nucleic acid (i.e., the target nucleic acid containing cystic fibrosis gene taught by Song *et al.,*) during the process for performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because Nerenberg *et al.,* suggest their method is used for the accurate detection of diseased states, especially clonal tumor disease states, neurological disorders and predisposition to genetic disease (see column 9, lines 43-46).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Response to Arguments

In page 25, second paragraph of applicant's remarks, applicant argues that "[C]laims 5-9, 17-20, 22-25, and 27 depend from claim 1 and are patentably distinct for the same reasons as applicable to claim 1. Therefore, Applicants respectfully request withdrawal of the rejections and reconsideration of the claims as amended".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because Nerenberg *et al.,* teach all limitations recited in claim 1 (see above Response to Arguments related to the rejection under 35 U.S.C 102).

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. No claim is allowed.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

October 12, 2006

FRANK LU
PRIMARY EXAMINER